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SOME PSYCHIATRIC ASPECTS OF NERVOUS SYSTEM INJURIES*

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THE variety of problems produced by nervous system injuries has become increasingly important with the progress of the war. This has called forth a careful appraisal, assessment and formulation of adequate treatment of the peculiar interrelating special surgical, neurological and psychiatric problems involved. This applies particularly to a large group of cases with a disability picture that is labeled "psychoneurosis" or belong to the group labeled "post concussion neurosis" or "compensation neurosis."

The varieties of post-traumatic reactions in terms of relationship between the severity and nature of the injury itself and the somatic and personality responses are often difficult to differentiate, to treat medically, and to rehabilitate socially and economically. It is hoped that the accumulated experiences of many workers now confronted with these problems will give us a more comprehensive knowledge and more efficient therapy with which to meet these situations in both military and civilian cases. Because of the difficulties encountered in differentiation of the traumatic and post-traumatic reactions, classifications of the psychiatric disturbances have not been too satisfactory. The military or war injuries introduce complications which differ in

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some respects from nervous system injuries sustained in civilian life. The combination of natural anxieties and tendency to worry or be concerned with prolonged war stress, sense of grievance, constitutional predisposition, malingering or the simultaneous development of a psychoneurosis under circumstances of exhaustion and fatigue, make for added confusion, particularly when there is also structural nervous system change.

In considering the symptoms of acute mental disturbance as a result of general cerebral injury, the most constant results of such injury from the psychiatric standpoint are the disturbances of consciousness. These range from states of transient interference in mild injuries to profound and prolonged states of coma in the most severe cases. Various grades of unconsciousness range between these extremes and for varying lengths of time.

The return from stupor or coma to normal consciousness is usually through a series of stages: coma, stupor, excitement or delirium, combativeness, aggressiveness, confusion and automatism. After full consciousness returns, the patient often is fully oriented but has a period of amnesia, frequently of a retrograde character or a mental haziness which dates from several minutes to hours prior to the injury and extends through until the final return to normal consciousness. This period or gap in the consciousness usually remains as a permanent defect. The return from the state of coma or stupor to consciousness may be associated from minutes, hours, days or weeks with states of semi-coma, confusion, motor activity and conversational ability but throughout the period there may be complete disorientation and inability to maintain sustained thought or expression. This state may be difficult to differentiate from other states of complete dissociation, particularly in the combat area, especially when there is no external evidence of a head injury.

In mild injuries momentary states of confusion or being dazed may be followed by an automatism like that described in cases of epilepsy or following electric shock therapy in which the individual may continue his activities either in a normal or abnormal manner and then may recall no part of them. This also, in the combat area, may lead to confusion, make for unintelligent behavior and totally incomprehensible actions. In injuries of this grade, then, an amnesia and automatism are the striking features.

In other types of mild injury without initial loss of consciousness there may be a form of delayed collapse after minutes or hours, some confusion of an in and out character, momentary blacking out, with or without automatism, supposedly due to an instability of the cerebral circulation consequent upon injury to its vasomotor apparatus, probably the result of damage to the brain stem.

In the severe brain injuries the individual is usually profoundly comatose and shocked. If he lives, coma eventually becomes less deep and the series of events already described begins and much depends not only on the concussion but on the individual's personality. With higher psychical functions temporarily suspended, the content of lower levels stands revealed, whether as a result of edema or from the effects of concussion itself. In these severe cases complete recovery does not always follow and signs of local damage are likely to be found and recovery may never reach the completely normal state. Specific defect disorders, emotional and cognitive changes may appear in the post confusional state.

Conscious activity comprises many different functions which must all be present before the behavior can be said to be normal. Any of these functions can be eliminated selectively by various types of brain lesions. Speech may be impaired by lesions in the temporoparietal area of the cortex. Lesions of the occipito-parietal area may give rise to other special defects. The same rule of breakdown and recovery after cerebral lesions applies to the other higher cerebral functions—memory, orientation, perception and imagination, and maintenance of emotional attitudes and stabile behavior patterns. Elimination of any of these functions resolves itself into a restriction of the background specific to that function. It is on the proper activity of this background that the function itself depends.

Apart from residual symptoms due to such local structural damage as has been mentioned, in some cases symptoms indicative of more general disturbance of cerebral function may persist for varying lengths after cerebral injury and may even be permanent. This is especially true in elderly and arteriosclerotic subjects, where some degree of mental defect is more apt to ensue. These defects express themselves chiefly as defects of memory and of judgment with impaired emotional control, easy fatigue of both attention and of physical effort. These symptoms frequently do not stand in any close relationship to the clinical

severity of the original injury.

As a rule most head injuries tend to recover completely and one infers that no structural damage has been sustained by the brain. In the others, however, it is difficult from then on to correlate persisting symptoms where recovery stops short of complete, as lesions may be present in the total absence of specific signs and symptoms. With the resources now available to us, disorders of cerebral function are more readily associated with discoverable and demonstrable lesions. Much recent outstanding work has been done towards assessing the severity of brain damage and is bringing us closer to more nearly accurate appraisals.

By far the commonest residual syndrome is that of headache, dizziness and emotional instability. This may persist for many months or for many years, is more apt to be long lasting in middle aged and elderly persons and often in patients whose injury is compensable or is carried on as a full expression of a psychoneurosis, sometimes of other origin than the cerebral trauma itself. Lesions in specific parts of the brain may facilitate neurotic reactions of the total personality and the organic consequences of head injuries may become the nucleus around which neurotic attitudes crystallize. The organic nucleus may be transformed, therefore, into that of the neurotic.

This suggests that in the syndrome or in the origin of the psychoneurosis, there is an interplay of physical and psychological factors. Unfortunately, the clinical criteria by which we might hope to distinguish psychogenic from physical elements in this symptomatology are by no means that distinct. At this time it is not considered possible to list or classify by any particular symptoms or criteria, for any symptom may have either psychoneurotic or organic basis, be due to diffuse degenerative change, focal or transient damage or be the expression of a latent psychoneurosis by a generalized physical effect.

Up to this point the psychiatric management of cerebral injuries should be confined to the needs of the immediate post-traumatic state. Very definite improvement in the procedures of management of head injuries in this war has been made soon after stabilization or clear consciousness is regained. Graduated programs of activity are frequently started within 24 to 72 hours after regaining consciousness with return to light duty in two weeks and full duty in six weeks time. One of the outstanding features in this early handling of these cases is the attempt

at complete divorcement from the idea that the injury is serious because it involves the head, that caution must be exercised from over-doing mentally and that such things as dizziness, headaches and nervous symptoms are to be expected. It also helps to eliminate the period of incubation in which the patient is meditating upon the suffering and derangement of his life caused by an accident for which, in most instances, he knows some one else may possibly be made legally responsible. The element of suggestibility by thoughtless reminders on the part of doctors and nurses can be potent factors. Furthermore, the Army hospital is not, as a rule, convenient for frequent visiting or any visiting by well meaning relatives, friends and claim agents who may be so helpful in building that post-traumatic crippled personality of civilian life. On the other hand, in an inaccessible theatre of military operations, treating a patient with head injury who may be emotionally unstable is not prognostically the same as the individual elsewhere, so that the element of secondary gain may be a potent factor in the production of a neurosis in the military theatre of operations. However, by and large, this new important step of immediate post-traumatic management and elimination of the incubation period has gained many converts among the neurosurgeons and neuropsychiatrists in this war.

The incorporation of convalescent and rehabilitation programs, the like of which is difficult to emulate in any civilian hospital, must be credited with much of the reversal of opinion regarding early post-trauma management of cerebral injuries when, not so long ago, prolonged bed rest, reduced physical and mental activity, restraint from duties for many months to a year was not an unusual prescription.

In this early activity phase there is introduced the psychological help calculated to strengthen the ego. Persuasion, strong suggestion, re-identification with the group, and stimulation of the ego-ideal result in an earlier return to active duty status before the stage of actual neurosis formation may be reached. Convincing reassurance, firmness in the pressure to return to duty and strong suggestion is most conducive to avoid binding anxiety to a symptom. Despite this, however, the physiological consequences of the trauma in many cases affect the function and structure of the brain to the extent that they offer material for the neurosis. The trauma brings about psychological change or activates latent or active neurosis of considerable severity. Fear of future ill health and unemployment are frequent natural factors.

When the elements of neurosis begin to dominate the picture the symptoms begin to assume bizarre qualities and to be complained of as being very disabling. Headaches not only become more continuous and fantastic but many other complaints are added. The emotional attitudes change and it is very difficult to explain the attitude perversions on the basis of structural damage to the brain. When these symptoms and changes become apparent, the time then has arrived to evaluate the symptoms and assess the role of psychobiological factors in the symptom complex.

At this point where the elements of a neurosis begin to dominate the picture we again find that there has been definite advancement in psychiatric management. Cases, particularly with anxiety and hysterical features, comprise a high percentage of these reactions, but almost any clinical expression of the psychoneurosis may become manifest. Our first duty is to strive for some appraisal of the physio-psychological aspects of the nervous system injury and attempt to estimate separately the organic residua and psychoneurotic symptoms. Just as in the medical and surgical treatment of nervous system injuries, each case must be studied and treated according to its particular merits. No injury is such a clinical entity for which a cut and dried line of treatment can be prescribed. This is also true of persistent after-effects.

In their order and when necessary, the following are indicated in the clinical evaluation at this point: (1) Painstaking neurological examination. (2) Evaluation of emotional factors and thorough attempt at a sound, rational understanding of possible conflict between the unconscious sources of anxiety and the ego forces together with an understanding of the symptoms produced by psychological defenses, regressions and collapse. (3) Psychological testing by specialized techniques, such as the Rorschach, Shipley-Hartford and others. (4) Electroencephalography. (5) Pneumoencephalography.

Some discussion of these evaluations warrant attention, particularly the evaluation of the emotional factors and methods for combating them. Again, we have profited by the experience of this war in the form of brief psychotherapy instituted in some theatres soon after the appearance of the traumatic neurotic expression, whether it follows injuries to the cerebrum or not. Narcoanalysis, narcosis therapy or narcosynthesis cannot be called exactly new since they have been used in civilian practice for the last ten years or so. Their free use, however,

has been necessitated and catapulted into the foreground by the urgent demands for quick brief therapy in the armed forces. This stands quite in contrast to the last war where rest, sedation and persuasion were chiefly used.

Actually, the application of this technique in prevention and treatment of neurosis following nervous system injuries has added to the understanding of the dynamic conflict between the unconscious sources of anxiety and the ego forces and to the evolvement of short term techniques derived from psychoanalytic principles. In this, time has been gained in that the period necessary to work through resistances in an effort to bring repressed emotions to consciousness has been eliminated. Likewise, uncovered anxieties can be tolerated without lengthy preliminary strengthening of the ego.

Conditions of war bring new factors to play upon the soldier's ego that are distinctly different from the conditions that prevail in civilian life as a result of accidents. The civilian traumatic neurosis occurs usually as a result of a single violent stimulus. The soldier, however, rarely develops his traumatic neurosis as the result of a single experience but as a result of accumulated stimuli, difficult physical conditions, intolerable environmental conditions, protracted separation from supporting and friendly human relationships and of sudden disruption of close personal ties with dead, wounded or injured comrades. The injury here is often the stimulus for a new and serious conflict with the ego ideal, inducing and provoking thereby the psychoneurotic expressions. Narcoanalysis followed by psychotherapy as the patient recovers from the narcosis results often in dramatic release of the unconscious psychological tensions, strengthens the ego forces and decreases the severity of the super-ego pressure. This has resulted in quick return to duty or combat or, at least, return to limited military service status, and in others it has offered the first steps to return to civilian life as useful members of society. This is particularly true of the cases with old latent anxieties and resentments dating back to civilian or early life periods.

Reactions of a depressed nature can be treated with convulsive shock therapy but must be carefully selected. This is another aid available in this war that was not at hand in World War I.

In the cases where it is difficult to distinguish the degree of physiological-psychological damage as a result of trauma, careful neurological examination must be relied upon and, just as the internist may turn to

the laboratory for a final decision, the neuropsychiatrist calls upon laboratory procedures for help. Psychological testing makes it possible almost always to differentiate between organic and psychogenic disturbances. Pneumoencephalography and electroencephalography in selected cases, and when indicated, may uncover definite positive findings of structural and physiological change as a result of the trauma.

These are the patients who require special consideration for their specific handicaps and are potential candidates for prolonged rehabilitation handling. Their worries about cure, livelihood, bodily helplessness and future disturbances of social and economic nature are real and offer a tremendous challenge and appeal for life in the future without dependency on the family or the country.

Another clinical picture presented by effects of injury to the cerebrum by concussion, shell, bomb or other explosion is that associated with subdural hematoma or effusion. The picture here is quite different qualitatively from the psychoneurosis with anxiety or hysterical states encountered after head injury. In the latter, extreme restlessness, motor activity, tension, nightmares and insomnia are prevalent. Noises, sounds of airplane motors, exhaust explosions are triggers sending them into profound anxiety. The subdural cases, to the contrary, present one of two syndromes.

In the most frequent syndrome there is marked retardation in intellectual activity and personality interrelationships. The facies is one of dulness with but little play of facial expression. The emotional tone is flat. Attention is impaired and responses are slow. Answers to questions are devoid of description and detail. The whole approach to life situations is one of superficiality and getting by without complicated mental activity. The patient may or may not complain of headaches but he is usually not dramatic in his complaints.

The less frequent syndrome occurs in those cases of subdural hematoma of longer duration and demonstrates the more classic picture usually associated with the organic reaction types. The most striking feature is the impairment of inhibition or restraint, producing a euphoric and sometimes facetious air. Motor restlessness with exaggerated mannerisms and gesticulations may be prominent. The emotional tone may be labile and explosive. There may be poor judgment, undue productivity, unusual expressions of hostility and lack of restraint. Definite organic intellectual defects in the form of distractability, memory fail-

ure, perseveration and repetition and circumstantiality may be present. Infrequent or minimal neurologic findings are the rule and as a result cases with subdural hematoma or effusion repeatedly are considered functional. Pneumoencephalography and psychological testing are often necessary for a final diagnosis and treatment by the neurosurgeons.

In yet another group there are the debatable cases where the relationship between head injury and mental disease is not so clear, other than that the trauma may serve as the immediate precipitating agent producing a delirium tremens, a schizophrenia, a neurosyphilis or manic depressive or other psychosis. A certain group of these mental changes bear only an indirect relationship to the trauma which acted as precipitant on a pre-existing psychopathic state rather than as the direct etiologic agent. On the other hand, there are a group of organic mental syndromes following brain injury that can be delineated as definite post-traumatic psychopathy in individuals who never had signs of psychopathic states before sustaining injury.

Before closing, a few remarks are in order concerning psychiatric aspects of peripheral nerve and nerve trunk injuries. Just as in cerebral trauma, injury to nerves may precipitate various types of neurotic behavior, either the organic consequences become the nucleus around which neurotic attitudes develop or latent psychoneuroses gain expression by the generalized effect of the trauma and the prolonged effects of convalescence, crippling and handicaping. The demands for capacity to adjust to new situations created in life by these handicaps may be very great. They may be influenced also by the phantoms that may follow amputations of either painless or painful character or may appear in unamputated paralyzed limbs deprived of sensation by injury to the nerves. These lesions force the realization in cases with amputations in accepting physiologically as well as psychologically the shortened limb. One of the great difficulties encountered in these cases is the failure to possess or develop a strong natural aptitude to elongate the limb at will in the use of tools very much like the individual who never succeeds in accepting or incorporating his artificial teeth. The competency of this aptitude for projection varies in different individuals, depending largely upon their stability and their inherent adaptive capacity.

Summary

Out of the war-time experience have arisen certain facts for em-

phasis. Many individuals developing disabling neurosis after head injury suffer from latent or active neurosis before exposure to military life or from neurosis incidental to the war experience. The patient's history frequently gives evidence of previous neurosis, psychoneurotic and neuropathic traits, unsatisfactory sexual adjustment, marked mood swings, seclusiveness, schizoid characteristics, extreme rigidity, excessive timidity, childhood fears, parental dependence, asocial acts, and previous psychological traumata. Individuals with such characteristics in their make-up should not be considered for either military or civil assignments where the elements of special danger and personal physical risks are great. Industry can well afford to profit by methods of selection of prospective employees for such jobs and positions similar in purpose to those used by the armed forces in selection of personnel for highly dangerous and hazardous undertakings, specifically such as in the flying and submarine branches of the service. Even if a psychiatric staff cannot be employed or provided, the development of psychologist selection staffs should be encouraged. The specific psychological tests and appraisals now available leave no excuse for haphazard selection of such employees.

Conclusion

In conclusion, several valuable psychiatric factors have been introduced in the management of nervous system injuries by the experiences of this war. Prophylactic psychotherapy during the management of the immediate post-traumatic phase had reduced persistent disability prospect. Application of short term techniques of therapy based on psychoanalytic principles, followed by sound rehabilitation programs has been most helpful in the treatment of nervous system injuries with subsequent neurotic expressions. Diagnostic and prognostic aids from psychological testing, electroencephalography and air encephalography may be necessary in the full appreciation of either structural damage or the psychoneurotic state. Those cases with mixed pictures of organic and functional disturbances require management according to the merits of their particular cases, either by prolonged psychotherapy, programs of rehabilitation or by the protective environment of institutional life.

THE PRESENT STATUS OF THE ETIOLOGY OF PRIMARY ATYPICAL PNEUMONIA*

COMMISSION ON ACUTE RESPIRATORY DISEASES**

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PRIMARY atypical pneumonia has been well recognized as a distinct clinical entity during the past six years.[1-3] Except in a small proportion of cases, the syndrome may be differentiated readily from the common bacterial pneumonias. Epidemiological observations have been made of the disease under conditions of endemic and epidemic spread.[4-7] The possible relationship of atypical pneumonia and undifferentiated acute respiratory disease has been pointed out by several investigators.[3-7]

Although the clinical and epidemiological aspects of primary atypical pneumonia have been quite well characterized, much uncertainty and obscurity still exist with respect to the cause of this syndrome. It has been recognized for some time that similar clinical illnesses may be produced by certain well-known agents. The relatively minor role of such agents in the production of atypical pneumonia as seen today, however, has not been emphasized.

We wish to present tonight a review of the present status of the etiology of primary atypical pneumonia and a summary of the studies carried out by the Commission on Acute Respiratory Diseases in an attempt to transmit this disease to animals and to human volunteers.

ATYPICAL PNEUMONIA CAUSED BY KNOWN AGENTS

The clinical syndrome of atypical pneumonia may be produced in

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its essential characteristics by a variety of agents, including bacteria, fungi, Rickettsia, and viruses.[1-3] An etiological diagnosis can be established in these cases by the use of procedures such as intradermal tests, isolation of the agent, and immunological or serological tests with the patients' acute-phase and convalescent-phase sera. When positive results are obtained, the illness must be considered as a pneumonia of specific etiological type and the diagnosis of primary atypical pneumonia should not be employed. In this respect, particular mention should be made of the psittacosis-lymphogranuloma or ornithosis group of viruses. Several recent publications have indicated that these viruses cause many cases of so-called primary atypical pneumonia.[8-17] While there is no doubt that localized outbreaks as well as sporadic cases of pneumonia due to these agents can occur, the data now accumulating indicate that the great majority of cases of primary atypical pneumonia are not caused by the psittacosis or related viruses.[6, 12, 18] During the past three years of the Commission's experience in the Army, the diagnosis of psittacosis or ornithosis has not once been established in a series of more than 500 patients with atypical pneumonia and other respiratory infections.

The bacteria, fungi, Rickettsia, and viruses known to produce pneumonia must therefore be sought and excluded as a cause of illness in any study of primary atypical pneumonia. It now appears to be established, however, that all of these known agents taken together account for an exceedingly small proportion of the total number of cases diagnosed as primary atypical pneumonia, in civilian as well as in military populations.

Primary Atypical Pneumonia of Unknown Cause

Extensive investigations have been carried out during the past few years in a number of laboratories in an attempt to transmit primary atypical pneumonia of undetermined cause. In most of the work laboratory animals of various species have been employed. Isolation of the causative agent has been claimed or implied in several recent publications.

Animal experimentation. In 1939, Stokes, Kenney, and Shaw[19] reported the transmission of a pneumotropic agent from the sputa of patients with atypical pneumonia to ferrets and mice. Unfortunately the agent was lost after several passages in mice and its serological relationship to the patients' illnesses was not established. The following

year Weir and Horsfall[20] reported the recovery from patients with acute pneumonitis of a virus causing pneumonia in the mongoose. Experiments with other animal species yielded negative results. The specimens employed were obtained from patients whose illnesses were consistent with a diagnosis of primary atypical pneumonia. The agent could apparently be maintained in chick embryos without the production of lesions. On transmission in the mongoose, lesions were produced with some irregularity. Neutralization with convalescent sera of the patients could not be obtained on initial inoculation of serum-virus mixtures, but was evidenced from a lower percentage of lesions in the mongooses by serial passages, in contrast to the results when acute-phase serum-virus mixtures were employed.

It may be of significance that the above two investigations were carried out on cases occurring during a period when atypical pneumonia attracted the attention of physicians in several Eastern cities.[21-23] While it is likely that recognition alone accounted for the reported prevalence of the disease, it is also possible that the cases were unique etiologically.

In the past three years several other reports have appeared. Blake, Howard, and Tatlock[24] isolated a pneumotropic agent from cats ill concomitantly with human cases of atypical pneumonia in a single household. Neutralization tests, though incomplete, suggested that the human and feline illnesses might have been due to the same agent. Baker[11] likewise isolated an agent from feline pneumonia and suggested its causal relationship to human atypical pneumonia. Baker's agent, however, subsequently proved to be a virus of the psittacosis-lymphogranuloma group.[15,25,26]

By the intranasal inoculation of cotton rats with sputa from cases of atypical pneumonia in the Army, Johnson[6] obtained pulmonary lesions. On passage of the lungs of these animals, however, lesions failed to persist with any degree of constancy.

Eaton, Meiklejohn, Van Herick, and Talbot[27,28] also found lesions in cotton rats and hamsters inoculated with sputa and lungs from patients with atypical pneumonia. More consistent results were obtained by the inoculation of chick embryos with material from the patients and subsequent inoculation of cotton rats and hamsters with the chick embryo tissue. Using this technique, it was found that convalescent sera from patients with atypical pneumonia prevented the production of lesions by the chick embryo tissue in most of the animals.

Horsfall and his coworkers[29] likewise obtained lesions by direct intranasal inoculation of cotton rats with sputa from certain cases of atypical pneumonia, but the lesions were not maintained on passage. These investigators further found that many of the animals, if permitted to survive, developed neutralizing antibodies for the pneumonia virus of mice.[30] Convalescent sera from patients with atypical pneumonia, when mixed with the sputum prior to inoculation, prevented the development of such antibodies, although these sera themselves contained no antibodies to the mouse virus. It was subsequently found[31] that antibodies to the pneumonia virus of mice could be stimulated non-specifically in cotton rats by inoculation of substances such as broth. Thus the appearance of these antibodies may well result from evoking a latent virus, but the ability of convalescent atypical pneumonia sera to prevent the development of the antibodies remains an unexplained observation.

Rose and Molloy[32] reported the occurrence of pulmonary lesions in newly-weaned guinea pigs inoculated intranasally with specimens from patients ill with atypical pneumonia. Immunological confirmation of the relation of such lesions to atypical pneumonia could not be obtained however, and Rose[33] now holds the opinion that no causal association exists.

Sanders[34] has isolated a virus in tissue culture and mice from the sputum of a case of atypical pneumonia. The virus produces a fatal encephalitis in mice but fails to cause pulmonary lesions. A strain of this virus, kindly supplied by Major Sanders, has been studied in the Commission laboratory. The development of antibodies to this agent during the course of atypical pneumonia could not be demonstrated by the neutralization test in mice. The agent appears to be a variant of the herpes virus.

An unusual combination of immunological reactions can be demonstrated with convalescent sera from cases of atypical pneumonia. They are, first, cold hemagglutination; second, fixation of complement with a variety of dissimilar antigens; third, prevention of the development of antibodies to the mouse pneumonia virus; and last, agglutination of an indifferent streptococcus. In general, the reactions are found with greatest constancy in sera from the most severely ill patients.

The development of cold agglutinins for group O human erythrocytes in the sera of patients with primary atypical pneumonia has been reported by a number of investigators.[35-40] The proportion of cases

showing this reaction has varied in different series from about 30 per cent to almost 100 per cent, depending in all probability on the factors of selection which entered into the availability of the cases. In an Army hospital, for example, a large number of patients with atypical pneumonia have such mild illnesses that they would not be hospitalized in civilian life. Thus far, no clues to the causative agent of atypical pneumonia have been afforded and substantiated by the reaction of cold hemagglutination.

Thomas and his co-workers[41] have reported that the sera of certain patients convalescing from primary atypical pneumonia have the capacity to fix complement with a variety of antigens, particularly those consisting of fresh suspensions of tissue. Fixation occurred with suspensions of various organs from different animal species, regardless of whether the animals were normal or infected with one of several viruses. These results have been confirmed on a limited scale in the Commission laboratory.

The capacity of convalescent sera of cases of atypical pneumonia to prevent the development of antibodies to the pneumonia virus of mice in animals inoculated with sputum[29] has already been discussed.

In 1943, Thomas and his co-workers[42, 43] at the Rockefeller Institute reported the isolation of an indifferent streptococcus from lungs and sputa of certain cases of primary atypical pneumonia. This organism is agglutinated by convalescent-phase sera from some patients with atypical pneumonia. It is closely related immunologically to *Streptococcus salivarius*, type I[44] and owes its serological reactivity primarily to a capsular polysaccharide. The organism in pure culture is not pathogenic for experimental animals. Cross-adsorption tests have shown that the agglutinins for the streptococcus are distinct from cold agglutinins for human group O erythrocytes. At the present time, the role of the bacterium in the causation of primary atypical pneumonia is obscure.

The convalescent sera of many cases of primary atypical pneumonia thus have the capacity to react immunologically in a variety of ways and with grossly dissimilar antigenic substances. While it is possible that these substances all have antigens in common with the causative agent of atypical pneumonia, yet another tenable hypothesis is that the various reactions reflect an alteration in the serum proteins and their reactivity, which is demonstrable non-specifically.

Repeated attempts to detect or isolate the causal agent or agents of

primary atypical pneumonia have been made in the Commission laboratories during the past three years. Throat washings, sputa, and blood from more than sixty cases of atypical pneumonia have been utilized. In addition, lung, spleen, brain, and other tissues from six fatal cases have been studied. In so far as possible, bacteria, fungi, Rickettsia and known viruses were sought for and excluded as causative agents in these cases.

Throat washings, sputa and lung have been subjected to fractional ultracentrifugation. The various fractions so obtained have been used in animal experiments as inocula, and in complement-fixation tests as antigens with acute-phase and convalescent-phase sera from cases of atypical pneumonia. The results failed to indicate the presence of any specific agent. Examination of the fractions with the electron microscope revealed no characteristic particles not also found in control specimens.

Extensive animal experimentation has been done, employing various routes and methods of inoculation, with and without adjuvants, such as mucin. No agents which could be related definitely to the human disease have been isolated in chick embryos, chickens, doves, Java ricebirds, mice, guinea pigs, ferrets, rabbits, dogs and three species of monkeys. Similar negative results were obtained with cotton rats and kittens. A series of experiments[45] employing the mongoose as the experimental animal has been carried out in the Antilles Department Medical Laboratory in Puerto Rico with the collaboration of Major G. J. Dammin and Captain T. H. Weller. Throat washings from seven cases of primary atypical pneumonia, sputa from six cases, lung from two fatal cases, and control specimens were inoculated intranasally and passed serially in a total of 265 mongooses. An agent was not isolated, nor could clinical or pathological evidence of pulmonary infection be demonstrated in these animals.

A great deal of the animal experimentation in the Commission Laboratory has been difficult to interpret due to the occurrence of nonspecific or spontaneous pulmonary lesions following intranasal inoculation and passage. At times, latent agents which could be identified have been evoked, such as the pneumonia virus of mice and viruses of the psittacosis-lymphogranuloma group. At other times, lesions have appeared in one passage, only to disappear completely on subsequent passage of those lungs. Extensive controls have been employed and in no instances have lesions appeared following inoculation of material from

patients with atypical pneumonia, which could not be duplicated in control series.

Thus, the occurrence of non-specific lesions and possibly the evocation of latent agents may account for much of the confusion and conflicting reports in the literature regarding the causative agent of primary atypical pneumonia. At all events, it would appear that detailed control series must be employed at all stages in animal experimentation—not only for attempting isolation of an agent, but also for relating the agent so obtained to the human disease.

Human experimentation: In view of the equivocal results in animal investigations, it seemed desirable to study experimentally the transmission of primary atypical pneumonia in the natural host, man. One such study has been reported. Vance, Scott, and Mason[46] were unsuccessful in transmitting the disease to seven volunteers by intranasal inoculation with filtrates of sputa and nasal washings.

The experiments summarized below have been carried out in human beings to determine (a) whether or not the disease is transmissible with secretions of the respiratory tract of ill patients, and (b) whether or not bacteria-free filtrates of such secretions are capable of inducing infection. The subjects were conscientious objectors who volunteered after the nature of the investigation had been completely explained to them.

The first experiment[47] was conducted in October, 1943, in a Civilian Public Service camp near Gatlinburg, Tennessee. A roentgenographic survey of the entire personnel of the camp failed to reveal any cases of atypical pneumonia. Accordingly, fifteen volunteers were placed in group isolation in the camp's infirmary. During the next five days, the men were examined daily for evidence of respiratory disease. Three individuals developed mild, afebrile upper respiratory infections during this time and were not inoculated. None of the three developed evidence of pulmonary involvement at this period or subsequently. Despite this complication, the remaining twelve men were inoculated with a pool of untreated sputa and throat washings from seven cases of atypical pneumonia. The sputa and throat washings were mixed and sprayed from an atomizer and nebulizer into the nose and pharynx of each volunteer, synchronizing the spraying with his inhalations.

Respiratory illnesses developed in ten of the twelve volunteers inoculated. These illnesses varied in their clinical characteristics, severity, and course. In two of the men the infections were mild, without fever.

In the remaining eight cases, fever developed from approximately 7 to 22 days after the inoculations. Three of the eight showed no evidence of pneumonia at any time, but characteristic "sticky," subcrepitant rales were present in the lungs of 5 patients. The roentgenograms of three of these patients showed minimal patchy infiltration in one or both lower lobes, and their illnesses were consistent clinically with moderately severe atypical pneumonia. The illnesses of the other two patients were similar to those considered as "suspected atypical pneumonia" or "bronchitis resembling atypical pneumonia," in that the clinical illness and physical signs were characteristic of atypical pneumonia, but pulmonary infiltration was not demonstrable roentgenographically. The sera of three of the men showed cold agglutinins in titers of 64, 128, and 256, respectively, during the course of their illness. None of the patients developed agglutinins for the indifferent streptococcus or antibodies for the influenza viruses.

These preliminary results were encouraging, even though interpretation was complicated, first, by the occurrence of mild respiratory infections in three of the group before the time of inoculation, secondly, by the possibility of cross-infection among the twelve inoculated men, and, lastly, by the failure of any of them to develop pronounced pulmonary infiltration. None the less, the illnesses of three of the men, following inoculation, were clinically characteristic of atypical pneumonia, and no similar illnesses occurred in the other personnel of the camp during the period of the experiment. Moreover, the infections were neither similar to the common cold clinically,[48] nor to influenza clinically and immunologically.

The second experiment was carried out in June and July, 1944. Thirty-six volunteers were placed in isolation in individual rooms equipped with private baths on the 2nd and 3rd floors of a 75-room hotel. Quarantine was instituted to prevent chance exposure to atypical pneumonia through outside contact, and was maintained for a period of three weeks prior to inoculation, since the available evidence suggested this interval as the maximal limit of the incubation period. The usual isolation techniques of a contagious hospital were instituted and maintained. Complete examinations, including roentgenographic, electrocardiographic and laboratory studies were done. The men were observed on alternate days for symptoms and signs of respiratory infection. Any one with acute or chronic organic or infectious disease was rejected.

After three weeks of isolation and observation, the men were inoculated in three groups of twelve persons each, as follows: (a) untreated throat washings and sputa pooled from seven cases of primary atypical pneumonia, (b) the same material, filtered through sintered glass and Seitz filters, and (c) the same material, autoclaved. The inoculations were made on a single day, utilizing first floor rooms located in one wing of the hotel as remote from the rooms of the volunteers as was possible. Three separate rooms, on the same side of the hall, were employed for the three types of inocula. Sheets, wet with cresol solution, were hung over the doors outside the rooms. The doors were opened frequently to admit entrance or exit of the volunteers and investigators.

Each man received a total inoculum of 10 ml. administered in three equally divided doses by spraying in synchronization with deep inhalation. The material was sprayed by three methods: hand atomizer, hand nebulizer, and an atomizer powered by a motor-driven air pump —the power spray commonly employed by otolaryngologists. The power spray was used first for the filtered material, secondly for the autoclaved material, and finally for the untreated inoculum. The equipment was sterilized between each set of inoculations, with the exception of the inner surface of the air pump on the power spray which was overlooked. The volunteers and professional personnel were masked and gowned in an attempt to prevent cross-infection or extraneous exposure. Precautions were taken to insure consistency and comparability in the inoculations of the three groups of men.

Ten cases of atypical pneumonia developed among the thirty-six volunteers. The cases varied in severity but all were characteristic of the disease as it has occurred in the Army. The following charts and brief case summaries will illustrate the essential character of the clinical illnesses and radiographic findings.

Cold hemagglutinin titers of 64 or greater developed in the sera of seven of the ten cases of atypical pneumonia during the course of illness. Agglutinins for the indifferent streptococcus, Rockefeller strain No. 344, developed during convalescence in the sera of two cases in a maximum titer of 32 from a pre-inoculation titer of <8. No change in titer was detected in the other eight cases.

Repeated attempts were made to isolate the indifferent streptococcus by culture from the volunteers both before and after inoculation. The organism was found in one-third of the men before inoculation and in

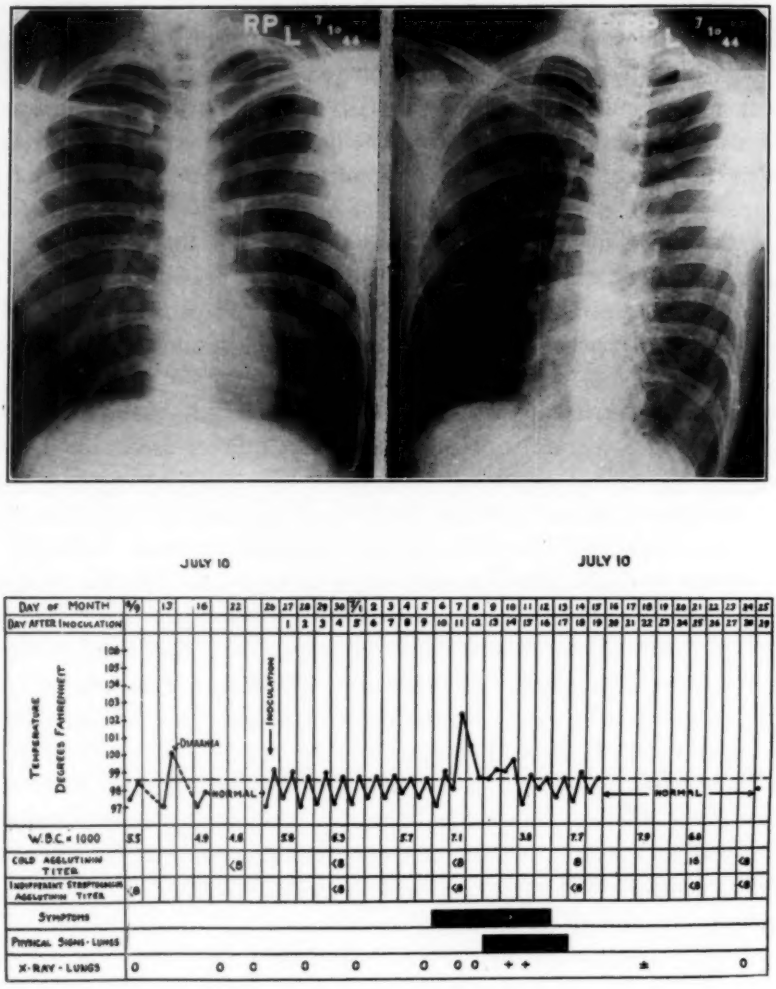
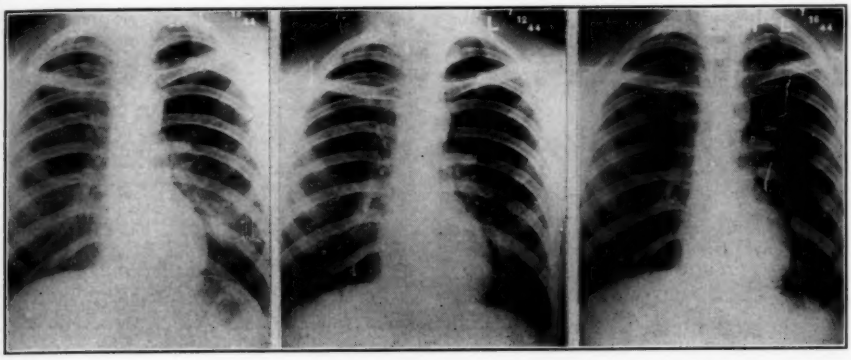


Figure 1—A mild case of primary atypical pneumonia. This patient experienced a mild episode of gastro-enteritis during the period of quarantine. Recovery was prompt and complete. On the tenth day after inoculation he developed mild atypical pneumonia, demonstrable by roentgenogram, in the left lower lung field. Cold hemagglutinins and agglutinins for an indifferent streptococcus (#344) did not develop. (Case No. 46)



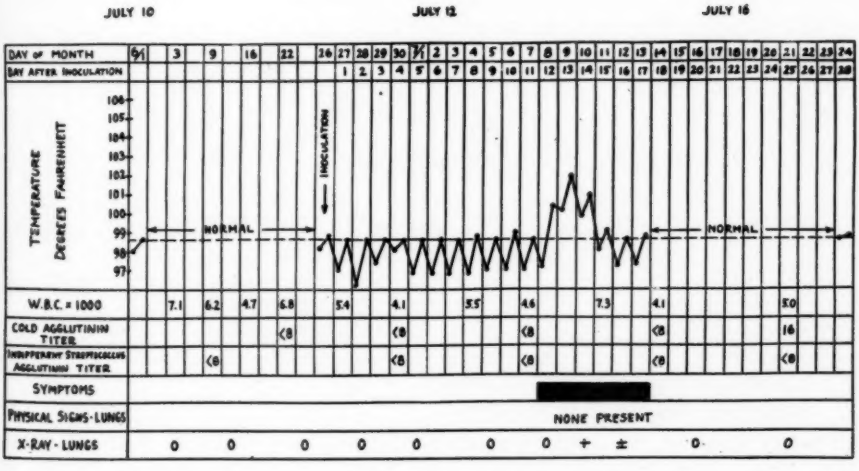


Figure 2—(Case No. 25). A mild case of primary atypical pneumonia. Mild atypical pneumonia began abruptly in this patient 12 days after inoculation. Roentgenogram on the 14th day (July 10th) showed a soft infiltration in the left lower lobe. No abnormal physical signs in the lungs were detected at any time. Neither cold hemagglutinins nor agglutinins for streptococcus #344 were detected in his convalescent sera.

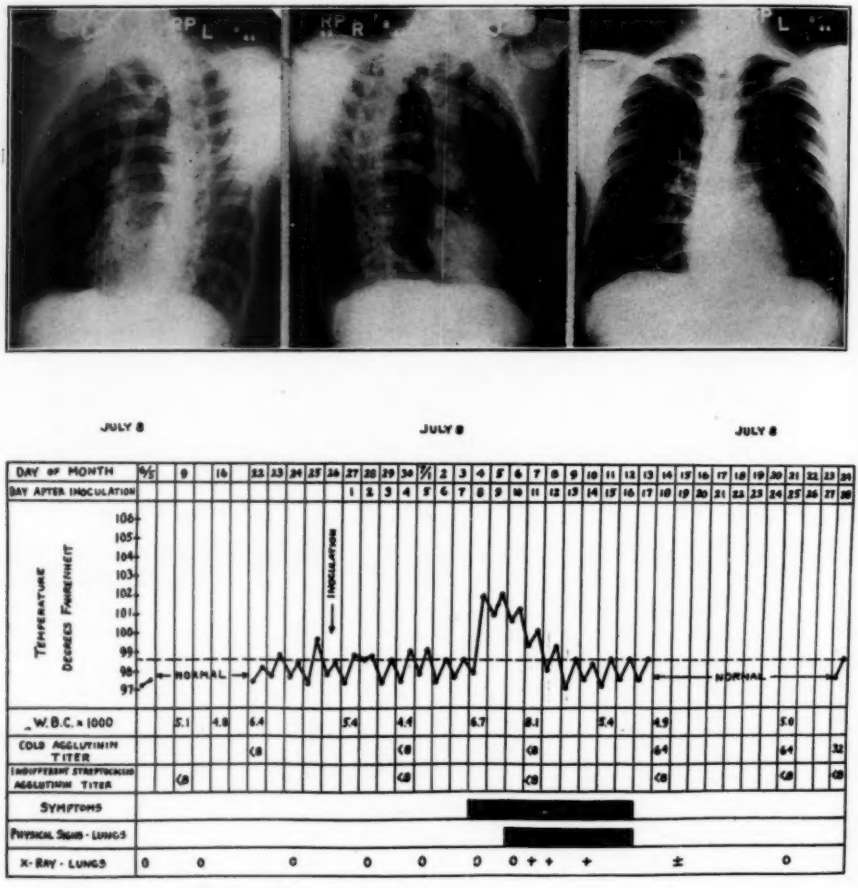
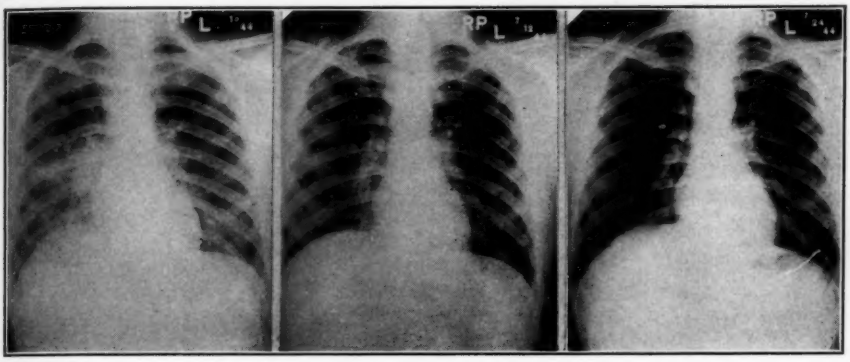


Figure 3—(Case No. 42). A mild case of primary atypical pneumonia with pulmonary infiltration visualized roentgenographically only in the right and left oblique positions. This patient experienced a mild attack of atypical pneumonia beginning on the 8th day after inoculation. Physical signs of pulmonary involvement were present in both bases. Areas of infiltration at the extreme lung bases were visualized roentgenographically only in the right and left oblique positions and were not visible in the conventional posterior-anterior films. Convalescent sera showed a maximum cold hemagglutinin titer of 64; agglutinins for the indifferent streptococcus were not found.



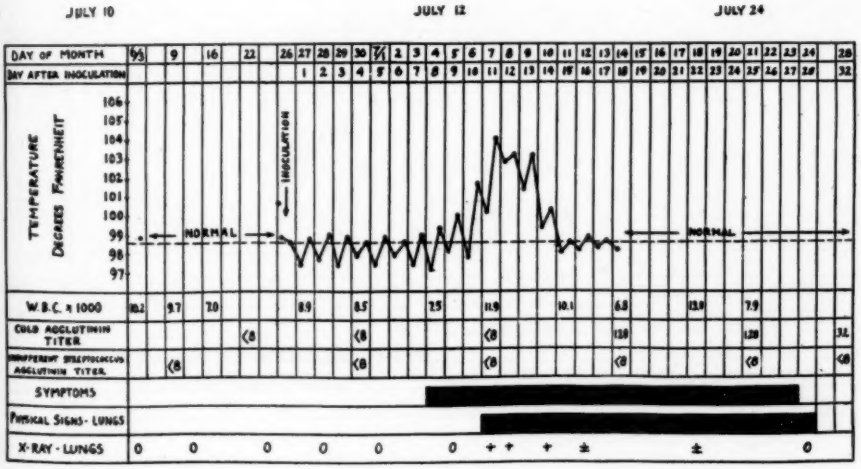
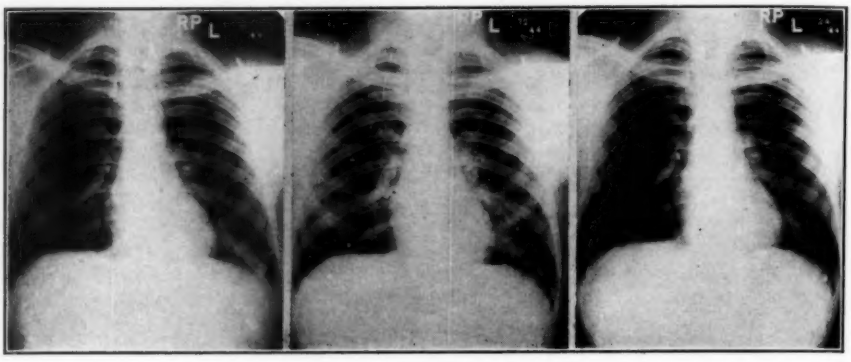


Figure 4—(Case No. 2). A moderately severe case of primary atypical pneumonia with involvement of the entire right lung and left lower lobe. Moderately severe atypical pneumonia developed in this patient 8 days after inoculation. The infiltration ultimately involved the entire right lung and the left lower lobe. Cold hemagglutinins developed to a titer of 128. No agglutinins for the indifferent streptococcus were demonstrable.



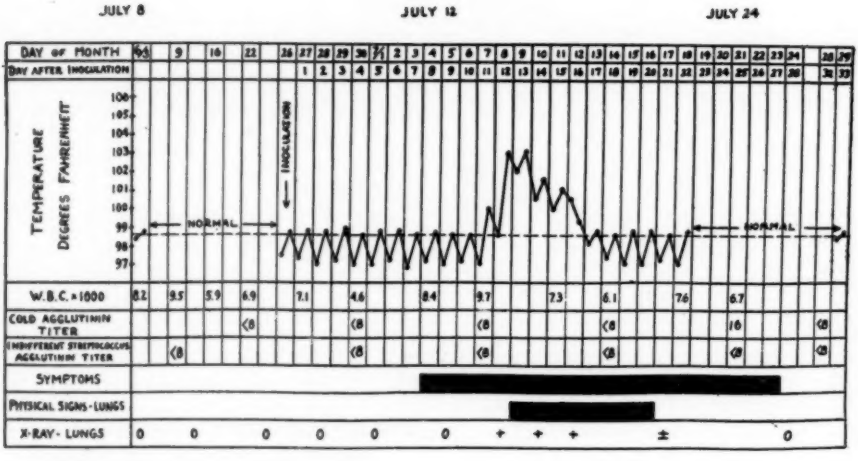


Figure 5—(Case No. 5). A moderately severe case of primary atypical pneumonia. This patient experienced moderately severe atypical pneumonia. Symptoms appeared 8 days after inoculation and the temperature became elevated 3 days later. Pneumonic infiltration appeared first in the left lower lobe and subsequently involved the right lower lobe. Abnormal physical signs were present at both bases. Neither cold hemagglutinins nor agglutinins for streptococcus #344 were found in the convalescent sera in significant titers.

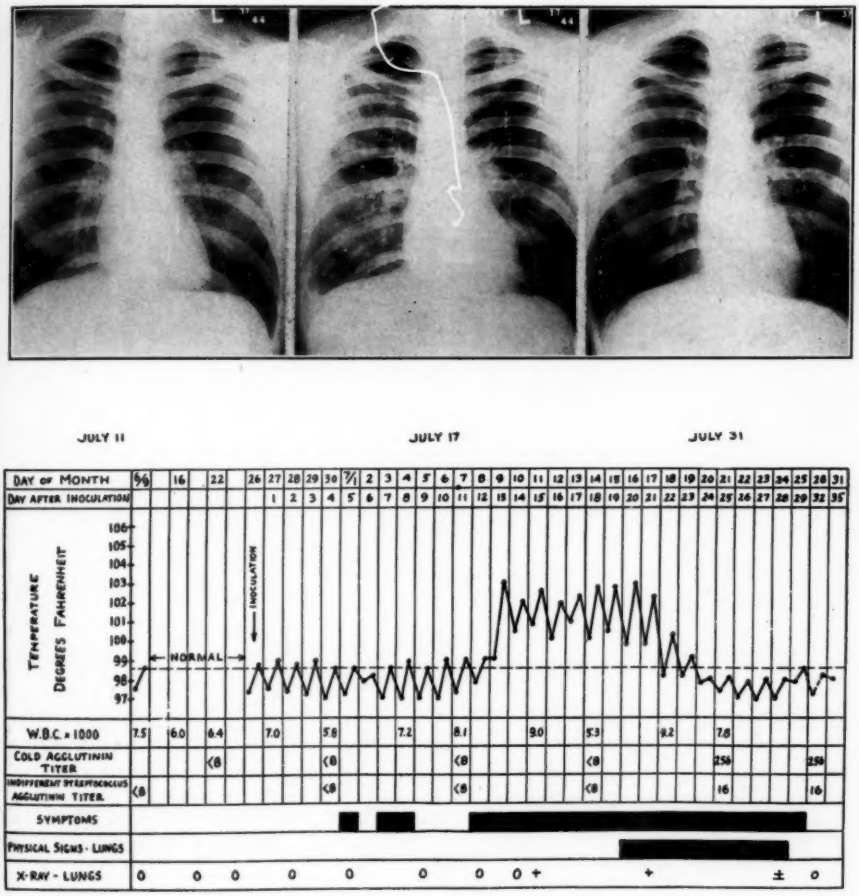


Figure 6—(Case No. 45). A moderately severe case of primary atypical pneumonia. After 2 intermittent periods of respiratory symptoms, this patient became ill with moderately severe atypical pneumonia on the 12th day, post-inoculation. Remittent fever persisted for 10 days. Patchy pneumonic infiltration of the entire right lung and left lower lobe were demonstrable in roentgenograms. Cold hemagglutinins were present in a maximum titer of 256 on the 25th day after inoculation, or 13 days after onset of illness. Streptococcus agglutinins increased to a titer of 16 at the same time and reached a titer of 32, 4 weeks later.

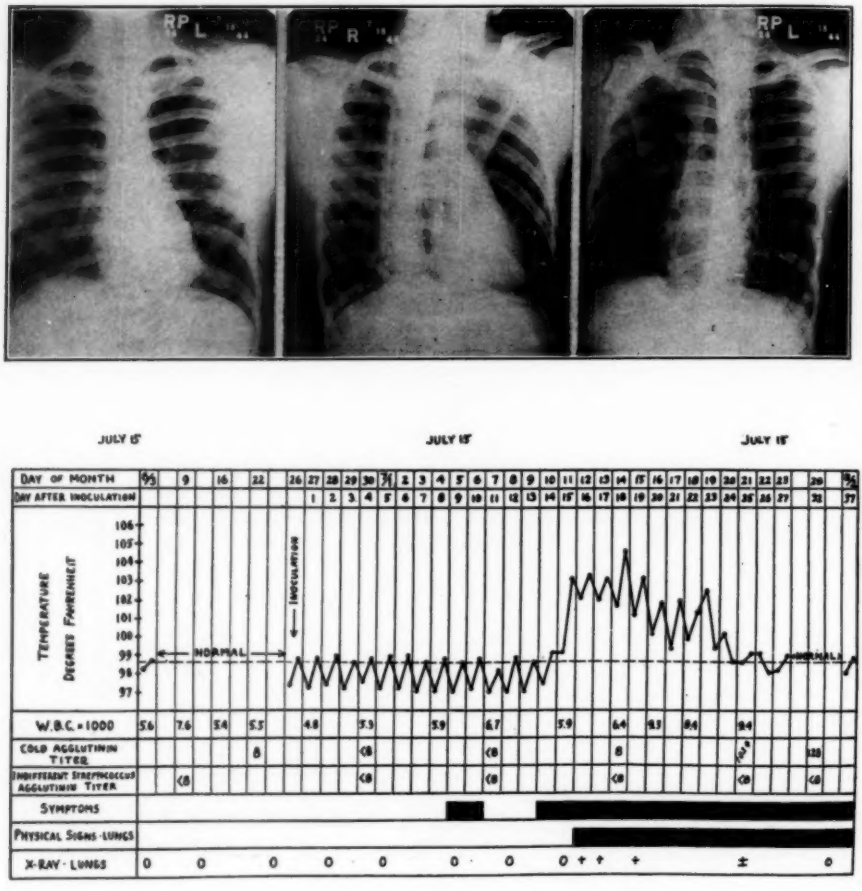
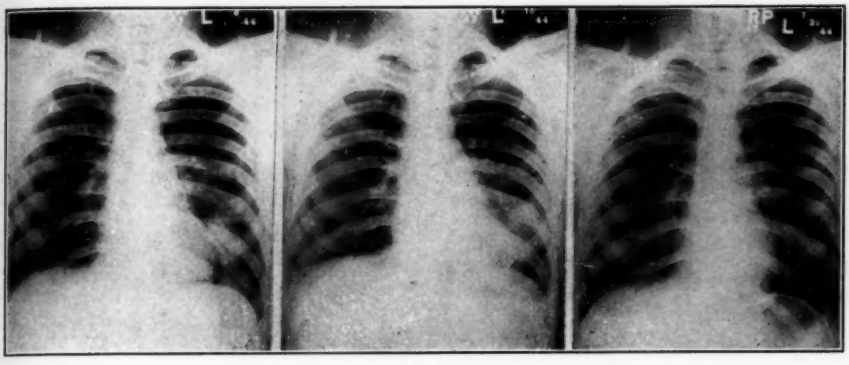


Figure 7—(Case No. 24). A severe case of primary atypical pneumonia complicated by disorientation and emotional instability. This patient's illness was characterized by high temperature and patchy infiltration at both lung bases on July 15th, the 19th day after inoculation. He was considerably sicker than the extent of his lesions would suggest. Following the peak of temperature of 104.6° F., disorientation and emotional instability were conspicuous features of his illness. Neurological examination revealed no abnormal findings, however, and the cerebrospinal fluid was normal. Recovery was complete. Cold hemagglutinins were demonstrable in a titer of 1024 on the 11th day after onset of illness. Agglutinins for streptococcus #344 were not found.



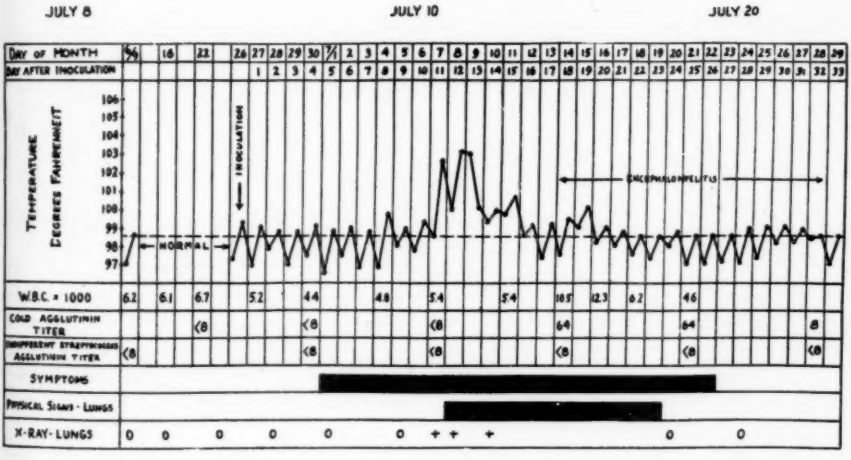


Figure 8—(Case No. 47). A relatively mild case of primary atypical pneumonia complicated by myeloencephalitis. This patient suffered from a relatively mild atypical pneumonia with involvement of the left lower lobe. On the 18th post-inoculation day, however, symptoms and signs of meningeal irritation appeared. Neurological findings indicative of diffuse myeloencephalitis developed during the succeeding days. Cerebrospinal fluid was clear and contained 17 small mononuclear cells per cubic millimeter. Chemical determinations were within normal limits and the fluid was sterile. Recovery was gradual but complete. The titer of cold hemagglutinins reached a maximum of 64; agglutinins for the indifferent streptococcus were not detected.

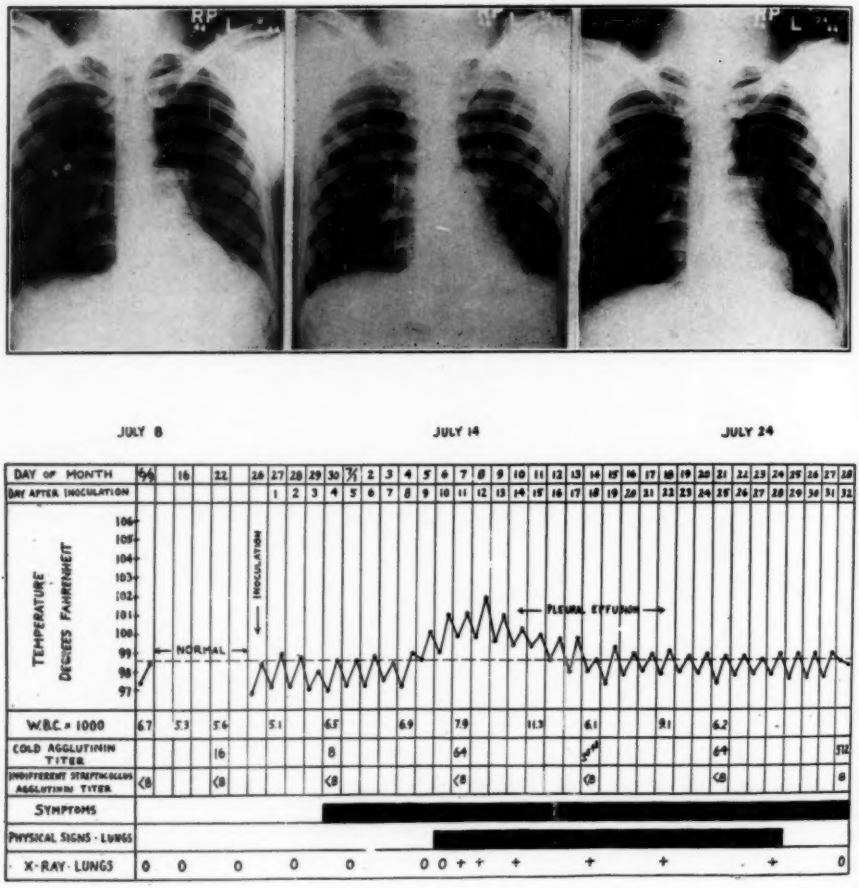
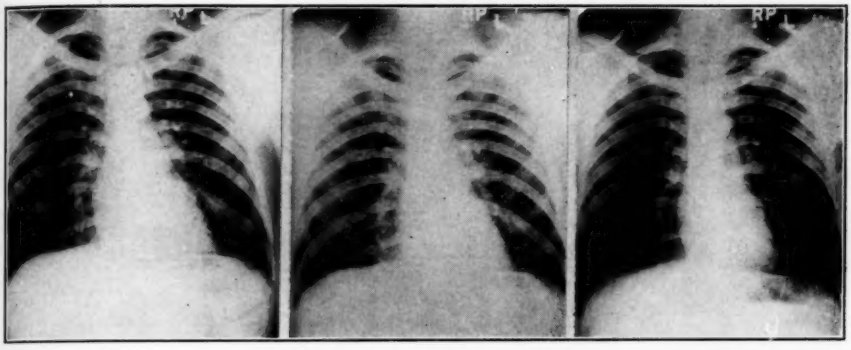


Figure 9—(Case No. 44). A relatively mild case of primary atypical pneumonia complicated by sterile pleural effusion. In this volunteer, atypical pneumonia, though relatively mild in character, was complicated by the development of pleural effusion at the left base. The fluid was sterile, greenish-yellow in color, and contained 1370 leukocytes and 240 erythrocytes per cubic millimeter. Approximately 55 per cent of the leukocytes were large mononuclear cells; the remainder were lymphocytes and neutrophiles. Cold hemagglutinins were present in the patient's serum in a maximum titer of 2048. Agglutinins for streptococcus #344 were not present in significant titer.



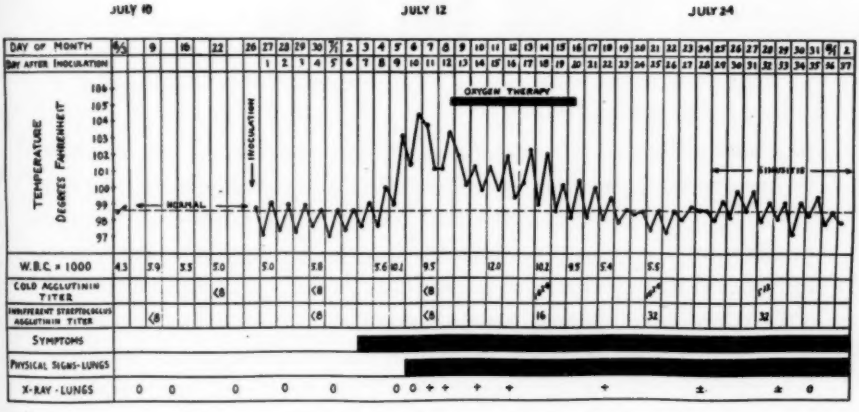


Figure 10—(Case No. 4). A severe case of primary atypical pneumonia with involvement of all lobes of the lung. This case represents the most severe atypical pneumonia in the group. Pulmonary infiltration appeared first in the right upper and middle lobes and subsequently extended to involve all five lobes. By roentgenogram a fine diffuse mottling was present throughout the lung fields. Oxygen therapy was required for approximately a week. Sinusitis occurred as a complication. Recovery was gradual but ultimately complete. Cold hemagglutinins and streptococcus agglutinins reached titers of 1024 and 32, respectively, in the convalescent sera.

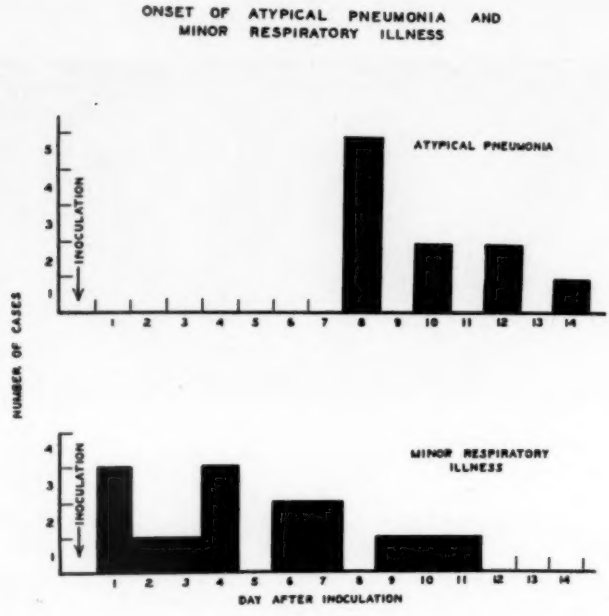


Figure 11.

one-half of them after inoculation, but the increase occurred with equal frequency in those who developed atypical pneumonia and in those who did not. There was, therefore, no apparent relation between the presence of this organism, either before or after inoculation, and the development of atypical pneumonia.

In addition to the ten cases of primary atypical pneumonia, there were fifteen cases of minor respiratory illness of undifferentiated type. The clinical onset of these cases, as well as that of the cases of atypical pneumonia, in relation to inoculation is shown in figure 11. For the purpose of this chart, the clinical onset of atypical pneumonia was defined as the day of development of *persistent* symptoms or signs which resulted in atypical pneumonia. The clinical onset of minor respiratory illness was defined as the day of development of any recognizable symptom or sign which was a definite departure from the normal state for that individual but did not lead to atypical pneumonia. This distinction was necessary because many of the minor respiratory illnesses were of short duration.

The clinical onset of atypical pneumonia, as thus defined, varied

TABLE I

PRODUCTION OF PRIMARY ATYPICAL PNEUMONIA AND MINOR RESPIRATORY ILLNESS IN HUMAN VOLUNTEERS INOCULATED WITH UNTREATED, FILTERED, AND AUTOCLAVED SPUTA AND THROAT WASHINGS FROM HOSPITALIZED CASES

Inoculum	*No. Men*	*RESULT*		
		AP	*MRI*	*No Illness*
Untreated	12	3	9	0
Filtered	12	4	5	3
Autoclaved	12	3	1	8
Total	36	10	15	11

AP—Primary atypical pneumonia.

MRI—Minor respiratory illness of undifferentiated type.

from 8 to 14 days after inoculation, whereas the onset of minor respiratory illness varied from one to eleven days. If the criteria used for minor respiratory illness were applied to the cases of atypical pneumonia, however, the onset of illness was between one and twelve days after inoculation. Whether or not these results indicate the presence of multiple agents capable of causing respiratory illness or merely mild illnesses or prodromata due to a single agent, cannot be determined at present. In none of the cases was there any change in bacterial flora, after inoculation or during illness, to suggest causation or even secondary bacterial infection. No serological evidence was obtained indicating infection with a virus of the psittacosis-lymphogranuloma group.

The results of this experiment clearly indicated that primary atypical pneumonia, and in addition, minor undifferentiated respiratory illness could be transmitted with secretions of the respiratory tract of patients with atypical pneumonia. Further analysis of the results, however, revealed that atypical pneumonia was apparently produced without regard to the type of inoculum (Table I), that is, three cases occurred with untreated inoculum, four with filtered inoculum, and three with the autoclaved material. The production of minor respiratory illness indicated greater specificity in that nine cases occurred with untreated

inoculum, five with filtered material, and only one with autoclaved inoculum. The interval between inoculation and onset of illness was in general shortest in the group receiving untreated sputa and throat washings.

A detailed review of all the conditions and procedures of the experiment was then undertaken in the hope of finding an explanation for the results. Numerous possibilities were considered but the three most likely explanations appeared to be (a) air-borne infection in the hallway on the day of inoculation, (b) contamination of the inner surface of the air pump for the power spray, and (c) the non-specific evocation of a latent agent. In support of air-borne infection was the occurrence of atypical pneumonia in an attendant who assisted in inoculating twelve volunteers with the untreated inoculum. Contamination of the air pump of the power spray could have been at least a contributing factor. During its first use with filtered inoculum, the air taken into the pump undoubtedly contained air-borne particles which were deposited on the inner surface of the pump. These particles could again have been liberated when the power spray was used with the autoclaved material. It is perhaps significant in this respect that, of the twelve men receiving autoclaved material, the three who developed atypical pneumonia were the first, second, and fourth in order of inoculation with the power spray. The possibility of non-specific evocation of a latent agent could only be determined by repetition of the experiment using extreme precautions against air-borne or other types of inadvertent "cross-infection."

The third experiment was then begun in August, 1944 as a repetition of the second, but with the following differences:

a. The inoculum consisted of pooled sputa and throat washings from 6 cases of atypical pneumonia in the second experiment, thus providing an opportunity for passage of the agent.
b. The inoculations were performed out-of-doors.
c. A tank of nitrogen was used as a source of pressure in place of the motor-driven power spray.
d. An interval of four days was allowed to elapse between inoculation of the autoclaved material and the filtered material. A second interval of 8 days elapsed before administration of the untreated inoculum.
e. Eighteen men were included in the group which received auto-

TABLE II

PRODUCTION OF PRIMARY ATYPICAL PNEUMONIA AND MINOR RESPIRATORY ILLNESS IN HUMAN VOLUNTEERS INOCULATED WITH UNTREATED, FILTERED, AND AUTOCLAVED SPUTA AND THROAT WASHINGS FROM EXPERIMENTALLY PRODUCED CASES OF ATYPICAL PNEUMONIA

Inoculum	*No. Men*	*RESULT*		
		AP	*MRI*	*No Illness*
Untreated	12	3	5	4
Filtered	12	3	5	4
Autoclaved	18	0	1	17
Total	42	6	11	25

AP—Primary atypical pneumonia.

MRI—Minor respiratory illness of undifferentiated type.

claved material to increase the possibility of demonstrating the evocation of a latent agent, if such were the cause.

f. The groups of men were segregated geographically within the building by construction of temporary partitions in the hallways.

In other respects, the essential conditions of the experiment were the same.

Six cases of atypical pneumonia and eleven cases of minor respiratory infection occurred in this experiment. Three of the cases of minor respiratory infection were diagnosed as "suspected atypical pneumonia" or "bronchitis resembling atypical pneumonia," because of the characteristic clinical course and physical signs, without roentgenographic evidence of pulmonary infiltration. In general, the illnesses were somewhat less severe than those in the preceding experiment, but in other respects they were entirely characteristic.

Distribution of the cases with respect to type of inoculum is shown in Table II. The untreated material produced three cases of atypical pneumonia and five cases of minor respiratory illness of which two were instances of "suspected atypical pneumonia." In the group of men receiving filtered material, there were likewise three cases of atypical pneumonia and five cases of minor respiratory illness, but only one of

the latter could be diagnosed as "suspected atypical pneumonia." There were no cases of atypical pneumonia among the eighteen men inoculated with autoclaved material, and only one instance of minor illness. This case occurred in the only man, to our knowledge, who broke isolation. On at least one occasion, he descended the fire escape to the room below which was occupied by a volunteer who subsequently developed a minor respiratory illness diagnosed as "suspected atypical pneumonia."

A striking difference was noted in the incubation period of the illnesses. The clinical onset of illnesses in the men receiving untreated material, with one exception (14 days), occurred between five and eight days after inoculation, whereas it was between nine and fifteen days, or almost twice as long, with the filtered inoculum.

The results of this experiment thus demonstrate that primary atypical pneumonia may be produced in human beings with filtered as well as untreated secretions of the respiratory tract of patients ill with this disease.

Discussion and Summary

An attempt has been made to review the present status of the etiology of primary atypical pneumonia. While a small proportion of cases presenting this clinical syndrome are due to known bacteria, fungi, or viruses, the cause of the majority of them remains to be characterized and identified.

The results of animal experimentation are confusing and difficult to interpret, due in large part to the lack of a truly susceptible animal, as well as to the complications introduced by the occurrence of spontaneous diseases causing pulmonary lesions in the animals employed. No work has yet been reported, and confirmed by other investigators in the field, which describes the isolation in animals of an agent clearly related immunologically to the human disease.

The experiments in human volunteers, summarized here, demonstrate that respiratory disease has been induced by the administration of sputa and throat washings of patients with primary atypical pneumonia. The clinical types of disease varied from the mildest of undifferentiated respiratory illness to classical severe atypical pneumonia. Between these extremes were cases resembling atypical pneumonia in onset, course, and physical findings, but lacking roentgenographic con-

firmation of pulmonary infiltration. Such cases were entirely similar to those observed on the respiratory wards of Army hospitals and diagnosed as "bronchitis resembling atypical pneumonia" or "suspected atypical pneumonia." The varied types of respiratory disease produced in these volunteers thus are consistent with the hypothesis previously advanced on the basis of clinical and epidemiological observations,[3-7] namely, that primary atypical pneumonia may be a severe form with pulmonary involvement of the same infection responsible for a large part of the more common, mild respiratory illnesses.

From these experiments some information may be gained regarding human susceptibility to respiratory diseases. Excluding the controls inoculated with autoclaved material, three-fourths of the men developed some type of respiratory illness and one-fourth had atypical pneumonia. In spite of the relatively large dose of 10 ml., one-fourth of the men had no illness whatsoever. Direct comparison of these figures, however, with attack rates observed in civilian and military populations is probably not justified because of lack of knowledge regarding minimal infecting dosage.

The question of the transmission of primary atypical pneumonia with bacteria-free filtrates of sputa and throat washings from patients with this disease was not easily answered. The results of the second experiment, in which atypical pneumonia was apparently produced with autoclaved inocula, permitted no conclusion regarding infectivity of the filtrates. They furthermore raised the question of non-specific evocation of a latent agent as the cause of the disease, as well as the possibility of inadvertent infection.

Accordingly, the third experiment was carried out utilizing extreme precautions against inadvertent infection and increasing to 18 the number of men in the control group, to strengthen the likelihood of detecting non-specific evocation. Sputa and throat washings from the previous experimental cases were employed as inocula to establish serial passage. The results demonstrated that primary atypical pneumonia could be induced with bacteria-free filtrates of sputa and throat washings as well as with the same inoculum before filtration. Autoclaved material, however, was without effect. It therefore appeared probable that the agent was filterable, that a latent agent was not evoked non-specifically, and that the cases following inoculation of autoclaved material in the prior experiment resulted from inadvertent infection. More-

over, from experimentally produced cases of atypical pneumonia, this illness as well as undifferentiated respiratory disease could again be transmitted to well individuals.

The length of time between inoculation and onset of illness may be of some significance, since this interval was almost twice as long in the cases receiving filtered inoculum as in those inoculated with untreated material. It is possible that such an increase in the incubation period is a function of dosage, and that filtration caused a considerable loss of the infecting agent. Another explanation is that bacteria act in conjunction with a filterable agent in the production of this disease. The failure to detect changes in bacterial flora following inoculation and during illness does not support, nor does it completely exclude, this concept.

The study in human volunteers thus leads to the conclusion that primary atypical pneumonia is at least initiated, if not caused, by a filter-passing agent, presumably a virus.*

* ACKNOWLEDGMENT—The members of the Commission wish to express their gratitude to the men who volunteered as subjects and attendants in the experiments reported here, and to the administrative staffs of Selective Service, the National Service Board for Religious Objectors and the American Friends Service Committee for the coöperation which made the studies possible. The Commission is indebted to Brigadier General H. C. Coburn, Jr., U.S.A., Colonel J. C. Williams, M.C., Colonel R. C. Tatum, M.C., Lieutenant Colonel F. J. Pohle, M.C., and Lieutenant Colonel F. K. Herpel, M.C., for their coöperation and assistance; to 1st Lieutenant Clara B. Kwash, A.N.C., 2nd Lieutenant Catherine E. Hammond, A.N.C. and Mrs. Catherine Kruse who served as nurses; and to Sergeant A. P. Aan, X-ray technician.

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CHEMOTHERAPY IN ACUTE UPPER RESPIRATORY INFECTIONS*

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THE topic assigned to me for this evening's discussion is a difficult one, chiefly because sufficient time has not yet elapsed for a thorough investigation of the possibilities of chemotherapy in upper respiratory infections. I take "chemotherapy" to mean the use of sulfonamides and penicillin. It is true that the sulfonamides have been widely used in the treatment of acute upper respiratory infections, but there is still considerable controversy among practitioners both as to methods and indications for the use of these agents. Penicillin has so recently been released for general civilian use that comparatively little is known about its value in coryza, influenza and their complications. We do know that penicillin possesses certain advantages that render it superior to the sulfonamides. Against susceptible organisms its antibacterial action is many times more potent than that of the sulfonamides. At the same time, even when it is administered in full therapeutic doses penicillin is entirely free of significant toxicity for the host. Unlike the sulfonamides, it is not inhibited by pus or the breakdown products of tissue autolysis. We know of course that most primary upper respiratory infections are of virus origin. It is also a fact that the great majority of viruses, including those causing coryza and influenza, are not subject to control by sulfonamides nor by penicillin.

It has generally been assumed that the complications of coryza and influenza are caused by secondary bacterial invasion, and it is true that cultures from such secondary infections as sinusitis, otitis, mastoiditis and bronchitis regularly yield one or more of the prevalent pathogens of the pneumococcal, streptococcal or staphylococcal groups. However, we need more thorough investigation of the bacteriology of these secondary infections. It has always seemed to me quite likely that the coryza or influenza virus not only attacks the nasopharyngeal mucosa,

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but frequently invades the adjacent tubes and cavities as well, thus preparing the way for secondary infection by a sort of symbiotic process. If this hypothesis is correct, it would explain some of the disappointments incurred with attempts to prevent or cure these complications by chemotherapy alone.

Let us now consider some of these infections in more detail.

Acute Coryza

The uncomplicated common cold is a mild infection caused by a filtrable virus which usually runs an afebrile course and clears up completely in four to seven days. Although it is generally recognized that virus infections are unaffected by sulfonamides, many practitioners and otolaryngologists have administered one of the sulfonamides to patients with the common cold with the idea of preventing complications. The practitioners have usually given the drug by mouth; the otolaryngologists have used a spray or powder locally in the nose or throat. Such procedure seemed quite rational and in individual cases the results often appeared to be beneficial. For example, Crowe and his associates[1] at Johns Hopkins Hospital treated a group of nurses with colds by spraying the throat and nasal passages with a 2.5 per cent sulfadiazine in 8 per cent ethanolamine solution (Pickrell's solution). In addition to symptomatic relief they observed a reduction in complications and a decrease in secondary bacterial invaders in the nasopharynx, particularly hemolytic streptococci. The nose and throat were sprayed from eight to twelve times a day for three days, and five to eight times a day for an additional three days. Some sinus involvement was noted in 30 per cent of the control group, whereas in individuals who were sprayed with sulfadiazine, sinusitis developed in only 9.7 per cent. Cough developed in 44 per cent of the controls; in only 8 per cent of the treated group. Some of the patients objected to the taste of the spray. Others complained of irritation of the skin around the external nares. Mild allergic symptoms developed in a small percentage of patients.

Rusk and van Ravenswaay[2] have recently published their results on the oral use of sulfadiazine in the treatment of acute febrile respiratory infections which were seen in a large Army station hospital during the winter of 1942-1943. Doses of drug (3.0 Gm. initially followed by 1.0 Gm. every four hours) similar to those used in pneumonia were admin-

istered until improvement occurred. In the 317 treated patients compared with 314 comparable controls the authors observed no significant difference in either the length of the febrile period or in the period of hospitalization. Contrariwise, Siegel[3] observed decided differences with and without sulfadiazine in alternate groups of feebleminded children with acute febrile respiratory infections, to which such individuals are particularly susceptible. In this reported series the incidence of serious secondary infections and the duration of the febrile period were considerably lessened.

In the winter and spring of 1942 the writer, in collaboration with Major Norman Plummer and Wilson G. Smillie[4] carried out some experiments on the use of sulfadiazine in the treatment of the common cold at the New York Hospital. The subjects of this study were all members of the personnel of the New York Hospital staff, including nurses, interns, orderlies and technicians. These patients were followed carefully with clinical examinations and nasal and pharyngeal cultures. Of these volunteers with acute respiratory infection, 48 received sulfadiazine by mouth for four days, while 24 received placebo tablets which could not be distinguished from the sulfadiazine tablets. Treatment was

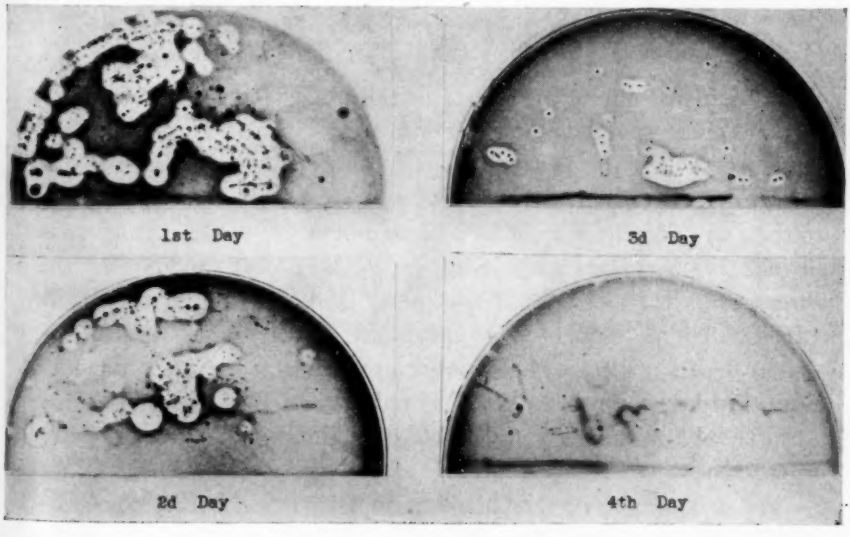

Fig. 1.—Decrease in normal nasopharyngeal flora following oral administration of sulfadiazine. Three grams daily for four days.

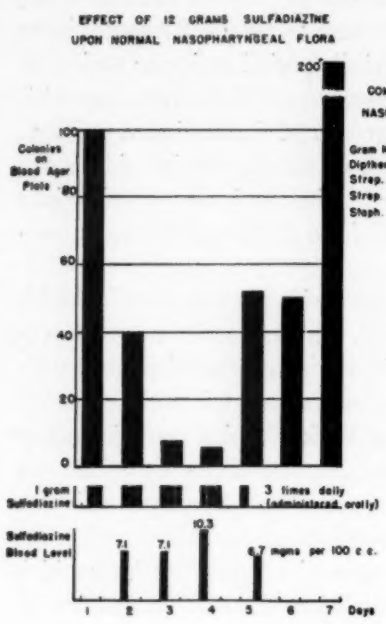

Fig. 2—Effect of 12 Gm. of sulfadiazine on normal nasopharyngeal flora.

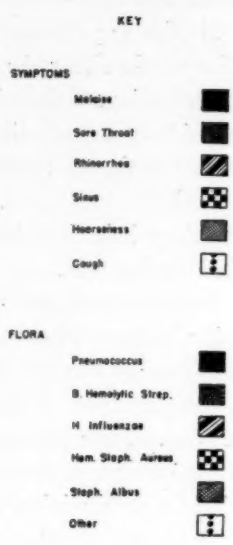

Fig. 3.—Key of symbols for symptoms and nasopharyngeal flora.

usually initiated during the second or third day of the cold. Sulfadiazine was taken in oral doses of one Gm. every eight hours for four days, or a total of 12 Gms. Nasopharyngeal cultures were taken at the time treatment was started and at regular intervals, usually every second to third day thereafter, in order to determine the changes that occurred in the nasopharyngeal flora following the treatment. Preliminary cultures on normal subjects indicated that on the dosage of sulfadiazine administered the blood level could reach 4-6 Mgm. per 100 cc. and that at this level there was pronounced reduction in the nasopharyngeal flora. Further cultures indicated a rapid return of the bacterial flora to its former prevalence and distribution within two to three days after sulfadiazine was discontinued.

Fig. 1 illustrates on four blood agar plates marked reduction in the normal nasopharyngeal flora following oral administration of sulfadiazine, 3 Gms. daily for four days.

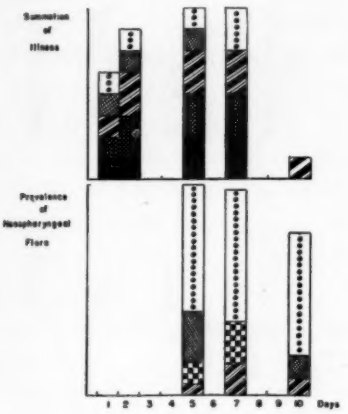

Fig. 4.—(M.H.) Control patient treated with milk sugar tablets. No change in pharyngeal flora; symptoms followed usual course.

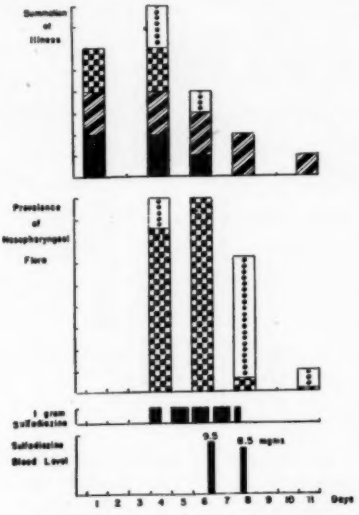
Summation of Illness
Prevalence of Nasopharyngeal Flora
1 gram Sulfadiazine
Sulfadiazine Blood Level
9.5
8.5 mgms
1 2 3 4 5 6 7 8 9 10 11 Days

Fig. 5.—(G.F.) This patient shows a favorable clinical and bacteriologic response to sulfadiazine treatment.

Fig. 2 shows the total colony count and correlates it with the blood level of sulfadiazine. This chart also illustrates the rapid return of the organisms to their normal pattern after discontinuance of drug treatment.

Fig. 3 is a key to the symbols used for designating the patient's symptoms and the character of the nasopharyngeal flora.

Fig. 4 represents the course of symptoms and the nasopharyngeal flora in a patient with coryza who received no sulfadiazine, but had milk sugar tablets instead. On the day of onset the usual symptoms of malaise, sore throat, rhinorrhea, hoarseness and cough were present. These symptoms persisted and increased somewhat in severity. The pharyngeal flora remained unchanged during the ten days of observation.

In contrast to this case is the one represented by Figure 5, a patient with coryza who received sulfadiazine treatment. The symptoms cleared up on the 7th or 8th day, and there was a marked numerical drop in the nasopharyngeal flora.

Figure 6 shows a patient with coryza treated with sulfadiazine on the first day of the infection. There was a marked numerical drop in

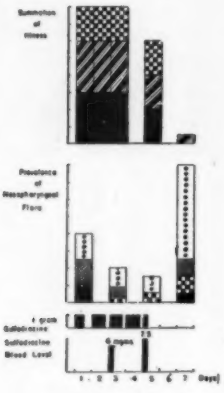

Fig. 6.—(B.P.) This patient shows excellent clinical and bacteriologic response to sulfadiazine but rapid reappearance of bacteria after discontinuance of the drug.

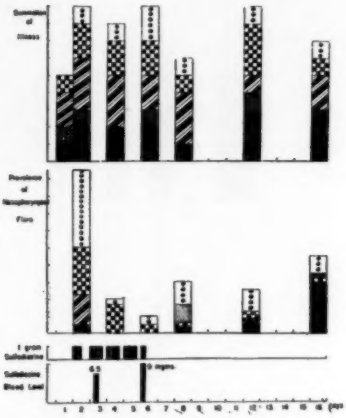

Fig. 7.—Acute coryza and sinusitis. Patient showed good bacteriologic response to sulfadiazine with only slight clinical improvement. With discontinuance of drug, pathogens again became numerous in the nasopharyngeal cultures, and patient developed a severe sinusitis and bronchitis.

the nasopharyngeal flora, but the symptoms persisted for three days and then subsided slowly, disappearing almost completely on the 7th day. When treatment was discontinued, the number of organisms increased, although there was no return of symptoms.

Figure 7 (S.M.) is the graph of a case of acute coryza which started with an irritated throat followed by malaise, rhinorrhea and sinus congestion. Treatment was started on the second day, when the rhinorrhea was severe and there was also an irritative cough. The nasopharyngeal culture on this day showed a heavy growth with a few colonies each of beta hemolytic streptococcus, H. influenzae and hemolytic Staphylococcus aureus. With the four days of treatment the course was somewhat favorable, the nasopharyngeal culture showing only a few organisms, the hemolytic streptococcus and H. influenzae disappearing entirely, and the symptoms being slightly less in evidence. With cessation of sulfadiazine treatment, however, the hemolytic streptococcus returned and type 20 pneumococcus appeared in increasing numbers. At the same time the symptoms became aggravated and the patient developed a severe sinusitis and bronchitis. The suggestion in this case is that if chemotherapy had been continued for a longer period

the secondary infection might have been prevented.

The illustrations cited above afford considerable evidence that sulfonamides do not alter the course of the uncomplicated cold. Furthermore, no outstanding benefits from sulfadiazine therapy were observed in colds complicated by sinusitis and bronchitis. It is quite clear, however, that secondary bacterial invaders can be eliminated or greatly reduced in number by sulfonamide therapy. Such being the case, it is rather surprising that sinus and bronchial complications would sometimes develop in the face of oral administration of sulfadiazine. Perhaps we made a mistake in not continuing the drug for longer than four days. The dosage used would certainly seem adequate, judging by the blood level.

Summarizing our clinical results, it must be admitted that they were not convincing. The average duration of the sulfadiazine-treated colds was 8.1 days, and that of the untreated colds 9.7 days. Of the 48 colds treated, 32 showed no recognizable secondary infection; 16 developed sinusitis, bronchitis or both, either during or after sulfadiazine treatment. Patients who developed complications, however, felt that they were milder in character than they would have been without the drug. The patients who received sulfadiazine were asked for their own opinions on the results obtained, and 34 expressed satisfaction with sulfadiazine treatment; 9 stated they noticed no difference from previous colds. The remainder had no opinion to offer.

Acute Pharyngitis and Tonsillitis

As far back as 1937 Long and Bliss[5] reported favorably on the oral use of sulfanilamide in the treatment of pharyngitis and tonsillitis. On the other hand, Rhoads and Afremow[6] in a controlled series of cases of pharyngitis and tonsillitis found that sulfanilamide did not lessen the severity of symptoms, reduce the incidence of complications or shorten the duration of the carrier state. Kernan[7] found that sulfanilamide orally did not alter the ordinary course of tonsillitis, but that complications were fewer when it was used. It seems quite likely that penicillin will replace sulfonamides in the treatment of streptococcal pharyngitis and tonsillitis. For hemolytic streptococcus sore throats I see no particular point in giving either sulfonamides or penicillin unless the infection is severe. In the severe streptococcal throats, either sulfadiazine or penicillin should shorten and mitigate the attack.

Major Norman Plummer writes: "We have had considerable experience with penicillin in the treatment of acute hemolytic streptococcal tonsillitis and pharyngitis. Undoubtedly penicillin is the superior drug against the hemolytic streptococcus and in conditions where there is an accumulation of pus."

Acute Sinusitis

Otolaryngologists are pretty well agreed on the value of the sulfonamides in acute sinusitis, especially in the fulminating sinus infections which are often caused by the hemolytic streptococcus. Bowers[8] prefers sulfadiazine or sulfathiazole powder applied directly to the mucous membranes. Silcox and Schenk[9] have used a 5 per cent suspension of microcrystalline sulfathiazole for the treatment of acute and chronic sinusitis, the suspension being instilled directly into the sinuses. In addition to the differences of opinion over the relative value and safety of the different sulfonamides in their crystalline and liquid forms, the value and safety of oral versus local administration also remains controversial. Again, as in the case of tonsillitis and pharyngitis, it seems quite possible that penicillin will displace sulfonamides in the treatment of acute sinusitis.

Chronic Sinusitis

In the treatment of chronic sinusitis there is considerable divergence of opinion on the value of sulfonamide drugs. Turnbull[10] reported that a large proportion of patients with chronic sinusitis were benefitted by spraying the nasal cavities with a 5 per cent solution of sodium sulfathiazole. No untoward effects were observed in Turnbull's series of 47 cases. This enthusiasm for the local use of the sulfonamides in chronic sinus infection has not been borne out by later reports, and there have been studies indicating that a 5 per cent sodium sulfathiazole solution is deleterious to the mucous membranes. At this point I would like to cite the case of the following patient who came under my care last summer, and which would seem to indicate that there is a place for penicillin in the treatment of some cases of chronic sinusitis. The local treatments in this patient were carried out by Dr. Stuart Craig.

The patient, Mrs. C., aged 60, had had chronic purulent pansinusitis for many years, accompanied by severe headaches which could be partially relieved by irrigations. The washings invariably yielded a

considerable amount of thick yellow pus which showed a pure growth of hemolytic Staphylococcus aureus. For the past year or two the patient had had considerable pain in the joints and muscles which possibly resulted from the chronic sinus infection.

On July 19th the patient was started on intramuscular injections of penicillin, 10,000 units every three hours, except for a midnight injection which was 15,000 units. The 3:00 A.M. injection was omitted. A total of 75,000 units of penicillin was administered each 24 hours, and this was continued for 14 days to a total of 1,000,000 units by the intramuscular route. Simultaneously the patient's sinuses received daily irrigation with penicillin in normal saline, 250 units of penicillin to each cc. of saline. In addition to the daily washing, the nose and throat were sprayed every two hours with a penicillin solution of similar strength. It was found that stronger solutions of 500 units to the cc. caused some irritation to the nasal passages, so they were discontinued.

After 14 days of this treatment the nasal mucosa was much less congested, the amount of secretion gradually diminished, and the character of the discharge had changed from a purulent to a mucoid character. Suction of the nasal passages brought down only a small amount of the material compared with the former large quantity. At the conclusion of two weeks, intramuscular injections were discontinued, but the nasal spray was kept up, the sinuses being washed out two to three times a week.

Three weeks later the headaches had practically disappeared and the mucous membrane presented a healthy pink appearance. A moderate amount of mucus was still discharged, however, from the sinuses.

On September 15th, two months after the institution of penicillin treatment, the mucous membrane still maintained its healthy appearance. The nasal mucosa was much less congested than on last note. There was a small retention still in the upper ethmoid of mucopurulent discharge. No headaches or pain in the sinuses or cranium.

Otitis Media and Mastoiditis

Otolaryngologists are in greater accord on the value of the sulfonamides in acute otitis media. Bowers[8] states that the necessity for mastoidectomy is reduced 50 per cent by the prompt use of the sulfonamides for otitis media, and this view is shared by many other laryngologists and internists as well.

Bronchitis

Acute and subacute bronchitis are common complications of coryza and influenza, and it is the opinion of the writer, based on considerable experience, that the severity and duration of acute bronchitis can often be mitigated by the use of sulfonamide therapy. Naturally this depends a great deal on the bacterial agent responsible for the bronchitis.

So far I have said very little about the use of penicillin for the very good reason that in acute upper respiratory infections my experience with the drug has been very limited. That of course has been the case with most civilian physicians. However, in some of the larger clinics penicillin has already been used experimentally in the treatment of these infections.

Because of the difference of opinion which exists as to the value of sulfonamides in acute upper respiratory infections and because of my limited experience with penicillin, I recently sent out a short questionnaire to twelve of my colleagues who have been particularly interested in the use of sulfonamides and penicillin in acute upper respiratory infections. Six were internists and six were otolaryngologists. All of these men were physicians who have had unusual opportunity to study these drugs in large metropolitan clinics. The responses were interesting and rather surprisingly consistent.

The first question was: "Do you advocate the use of sulfonamides in the treatment of uncomplicated coryza and influenza?" Eight of the 12 physicians gave an unqualified "No" to this question. Four otolaryngologists advocated the use of sulfonamides both locally and orally in severe infections with the aim of preventing complications. For local use, four of the otolaryngologists recommended Pickrell's solution, 2.5 per cent solution of sulfadiazine in 8 per cent triethanolamine solution.

2. Do you favor the use of sulfonamides in the treatment of acute sinusitis?

The response of all twelve to this question was "Yes", and 11 agreed that the drug was beneficial in shortening the course of the infection. One otolaryngologist expressed some doubt.

V. B. Hirst writes: "I have used the sulfonamide drugs locally in the treatment of sinuses with excellent results. The treatment has been with irrigation. In the past two or three years we have shortened the course of these cases very much, even the very foul types, and I am

sure have prevented a lot of surgery."

John Kernan writes: "At times the sulfonamides seem to work magic, especially on acute sinuses. However, much more careful checking should be done with cultures in order to select the proper drug to combat the particular organism involved in the case."

3. Do you favor the use of sulfonamides in *chronic* sinus infections, especially those of Staphylococcus aureus origin?

There was very little enthusiasm expressed by either the internists or the otolaryngologists for sulfa therapy in this condition. Practically all agreed that the results were very disappointing, and this was true whether the drug was used orally, as it was by the internists, or locally by the otolaryngologists.

4. Has oral administration of sulfonamides any advantage over the local use of the drug?

Four internists and four otolaryngologists preferred oral administration; four otolaryngologists employed both methods.

Walsh McDermott believes that oral administration has definite advantages. As he expresses it: "Sulfonamide is not an antiseptic solution, so must be taken up by the bacteria deep in the lesion. It seems to me the only way this could occur consistently would be if the blood supply of the infected lesion carried sufficient quantity of the drug. In addition, there is a strong suspicion, but no unequivocal proof, that local use of sulfonamides leads to increase of sensitization to the drug."

5. Do you advise sulfonamides as routine in the treatment of acute otitis media?

All answered "Yes", except one otolaryngologist who voted "No" because in his opinion they masked the onset of mastoiditis. The 11 who voted "Yes" were all convinced that the oral, or both oral and local use of sulfadiazine markedly reduced the incidence of mastoiditis and other ear complications.

Frank Horsfall writes: "Acute otitis media seems to me to be definitely improved, sometimes markedly so, by the use of sulfonamides in full therapeutic doses."

6. Will penicillin treatment shorten a cold?

Three answered "No". Four were in doubt. Five had had no experience with penicillin in the treatment of common colds.

7. Is penicillin of value in the treatment of acute sinusitis and acute otitis media?

Six physicians (four internists and two otolaryngologists) replied "Yes"; one said "No".

Francis Blake writes: "Penicillin will cure many cases of otitis that have failed to respond satisfactorily to sulfonamides. We have treated about 40 cases, the majority being due to Streptococcus hemolyticus, many with mastoiditis, some with beginning meningitis. The response has been almost perfect in hemolytic streptococcus infections, and very good in staphylococcus and pneumococcus infections. Penicillin was of no value in Hemophylus influenzae infections."

8. What success have you had with penicillin in the treatment of chronic sinusitis?

Two internists and one otolaryngologist replied "Good". Two otolaryngologists answered "Poor". One gave a qualified answer.

9. Have you used penicillin locally or parenterally for these infections?

Five internists had used the drug only by the parenteral route. One both parenterally and locally. The otolaryngologists have usually employed penicillin by both methods, though one had used it only locally. The dilution of penicillin for local use varied considerably, all the way from 100 units to 2000 units per cc. of saline solution. The tendency, however, was toward the weaker dilutions.

Stuart Craig writes: "The local use of sulfonamides, except in selected cases, is not outstandingly effective. The administration of even heavy doses for chronic cases with degenerative changes and thickened membranes has not proved effective in our hands. From the limited opportunity we have had to use penicillin locally in the sinuses, I would believe that it offers great promise when it can be used for the treatment of both acute and chronic sinusitis with no restrictions as to the amount available."

10. Have you seen allergic reactions, such as fever and drug rashes from the local use of sulfonamides?

Four internists answered "No". One had seen a few allergic reactions. It was interesting that 4 out of the 6 otolaryngologists replied "Yes" to this question, suggesting that reactions were more likely to occur from local than from oral use of the drugs.

Wesley Bowers writes: "It seems that we shall always have to bear in mind that using sulfa drugs for trifling conditions may render the patient sensitive to them, so that when they are badly needed for

meningitis or pneumonia, the patient would be forced to go without them."

Walsh McDermott writes: "I have seen allergic reactions in patients receiving sulfonamides by mouth who gave a history of previous use of the drug locally."

12. Have you seen allergic reactions following the use of penicillin?

Three internists replied "Yes", three "No". The otolaryngologists all replied "No".

McDermott says: "Febrile spikes as high as 40° C. have occurred following intramuscular injections of penicillin in previously afebrile patients. I have also seen two patients with definite serum sicknesslike syndrome following penicillin therapy, characterized by urticaria, periorbital edema, myositis, arthralgia and fever."

Summarizing the questionnaire, we can make the following fairly consistent generalizations:

1. There is little or no enthusiasm for the use of sulfonamide drugs for the treatment of the common cold and influenza. A few otolaryngologists recommend the drug to prevent complications, but they are in the minority.

2. Both internists and otolaryngologists are enthusiastic over the use of sulfonamide therapy in acute sinusitis. They are much less enthusiastic concerning such treatment in chronic sinusitis.

3. Practically all are agreed that sulfonamides are valuable in the treatment of acute otitis media as a means of preventing mastoiditis.

4. There is no enthusiasm for the use of penicillin for the treatment of the common cold, but there is almost complete uniformity of opinion that penicillin is of value in the treatment of acute sinusitis and acute otitis media.

5. There is only moderate enthusiasm for penicillin therapy in chronic sinusitis.

6. All are agreed that successful therapy with either sulfonamides or penicillin is in large measure dependent upon the type of bacteria responsible for the infection.

7. Allergic manifestations are occasionally seen with both sulfonamides and penicillin, usually in the form of an urticarial rash.

8. Oral administration of sulfonamides and parenteral injection of penicillin are favored over local application of these agents. Combined systemic and local treatment is also popular with both groups.

Comment

One fact seems to stand out clearly as a result of this discussion. There is no indication for the administration of either sulfonamides or penicillin in the treatment of ordinary coryza or grippe. As McDermott says: "With the ordinary cold I see no point in taking the risk of sulfonamides or the *discomfort* of penicillin."

In certain selected cases where the patient knows from past experience that his cold will probably be followed by some complication, one might be justified in using either sulfadiazine or penicillin, but even in these cases there is often some doubt as to the desirability of the procedure.

There is something quite Utopian about the eagerness with which both the medical profession and the laity search for a cold cure, yet when all is said and done, in the vast majority of cases, the common cold is a trivial infection. It makes us uncomfortable for a few days, but usually (with the help of aspirin, atomizers and Scotch whiskey!) we keep at our routine duties. There is a group of patients, of course, for whom the common cold is a much more serious problem. They know from past experience that complications in the sinuses or trachea are going to follow. In a good many children the middle ear has a rather terrifying way of lighting up with every coryza. It is in this group of patients that chemotherapy has its important field. The writer's own experience and that of the physicians whom he has consulted in this questionnaire indicate that sulfonamides and penicillin both have a place in the treatment of these complications. As we obtain more experience penicillin may prove to be the preferable agent. In fact it may entirely replace the sulfonamides.

I don't believe that chemotherapy would be generally successful in any sinus infection that was not at the same time receiving adequate surgical drainage. With drainage, chemotherapy, either sulfadiazine or penicillin, should be effective in properly selected cases. A good deal more investigation will have to be done before dogmatic answers can be arrived at. In the meanwhile it would seem the wiser course for the practitioner to limit his use of these agents to the treatment of sinusitis, otitis, bronchitis and the other less prevalent complications of acute upper respiratory infections.

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